The Biochemical, Histopathological and Clinical Comparison of the Neuroprotective Effects of Subcutaneous Adalimumab and Intravenous Methylprednisolone in an Experimental Compressive Spinal Cord Trauma Model

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ABSTRACT

AIM: To evaluate the neuroprotective effects of adalimumab in an experimental spinal cord injury model and compare them with those of the widely-used methylprednisolone.

MATERIAL and METHODS: Forty male Wistar rats were divided into 5 as the sham, trauma, adalimumab, methylprednisolone, and adalimumab+methylprednisolone groups. Only laminectomy was performed in the sham group. Laminectomy and trauma was performed to the trauma group but no treatment was given. A single dose of 40 mg/kg subcutaneous adalimumab was administered after the laminectomy and trauma to group 3. A single dose of intravenous 30 mg/kg methylprednisolone was administered right after laminectomy and trauma to group 4. Single doses of 40 mg/kg adalimumab and 30 mg/kg methylprednisolone were administered together after laminectomy and trauma to group 5. Serum malondialdehyde (MDA), TNF-α, IL-1β and IL–6 levels were measured and sections were obtained for histopathological study at the end of the 7th day.

RESULTS: MDA, TNF-α, IL-1β and IL–6 levels in serum were significantly decreased in the adalimumab group with clinical and histopathological improvement not less than the methylprednisolone group. The serum MDA levels were similar when the two drugs were given together or separately but there was a statistically quite significant decrease in TNF-α, IL-1β and IL–6 levels with concurrent use. Statistically significantly better results were obtained on histopathological evaluation with the use of both drugs together.

CONCLUSION: This study revealed that adalimumab is as effective as methylprednisolone in compressive spinal cord injury in rats.

KEYWORDS: Adalimumab, Methylprednisolone, Rats, Spinal cord injuries
INTRODUCTION

Spinal cord injury (SCI) is a significant clinical problem that can lead to persistent neurological deficits and secondary complications and decrease the quality of life. Primary mechanical damage cause by trauma to the spinal cord is followed by secondary damage with increased calcium and the release of excitatory amino acids, free oxygen radicals and many chemical substances such as TNF-α, IL-1, IL-6 and IL-8 (20, 22, 72). Medical treatment for traumatic spinal cord injury aims to prevent secondary damage (19, 21, 35, 69).

Models such as laceration (56), impact (57), clip compression (60) and dislocation (23) have previously been used to create experimental spinal cord injury.

The neuroprotective effect of many pharmacological agents such as methylprednisolone, melatonin, erythropoietin, magnesium, mexiletine, naloxone, infliximab, clotrimazole, lamotrigine and hyperbaric oxygen in experimental spinal cord injury has been studied (4, 13, 34, 37-40, 47, 75, 76, 80, 81). Among these substances, only methylprednisolone has entered clinical use (33) and it is the only agent proven to have positive effects after spinal cord injury. However, despite the beneficial effect on parenchymal damage, it has been shown not to provide a significant functional improvement (62).

TNF-α and pro-inflammatory cytokines such as IL-1β and IL-6 have been found to increase within hours after spinal cord injury and recent studies have revealed that these cytokines that increase in serum are directly related to persistent motor dysfunction and histopathological damage (26, 32, 68).

Malondialdehyde (MDA) that has an aldehyde structure appears after breaking of the carbon bonds during lipid peroxidation. Malondialdehyde is a final product in lipid peroxidation and MDA levels are used as an indicator of the level of oxidative damage. MDA plasma and tissue levels are measured as an indicator of free radicals (55).

Adalimumab (Humira®) is a human monoclonal TNF-α antibody drug and blocks the effects of TNF-α. It is used successfully at a dose of 40 mg/kg subcutaneously every 2 weeks in the treatment of disorders such as Crohn’s disease, ulcerative colitis, psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis (13, 14, 42, 43, 59, 65).

This study was conducted to evaluate whether adalimumab, an agent commonly used in rheumatology and gastroenterology disorders, has neuroprotective effects in an experimental compressive spinal cord injury model by assessment of histopathological changes in the traumatized tissue; serum MDA, TNF-α, IL-1β and IL-6 measurements; and clinical use of the inclined plane test and modified Tarlov’s Grading Scale. We then compared the results with those of methylprednisolone, another commonly used agent. This is the first study to investigate the neuroprotective effects of adalimumab in experimental spinal cord injury.

MATERIAL and METHODS

Experimental Groups

Approval was obtained from the Ministry of Health Ankara Training and Research Hospital Ethical Committee for the study. The surgical procedures of the study were performed at the Ministry of Health Ankara Hospital Experimental Animal Laboratory. A total of 40 adult male Albino Wistar rats (8 rats in each of the 5 groups) weighing between 250 and 300 g were used in this study. The rats were selected randomly and divided into 5 groups as the sham, trauma, adalimumab, methylprednisolone and adalimumab+methylprednisolone groups as follows:

- Group 1: Only laminectomy was performed to the 8 rats in the sham group; trauma (spinal cord injury, sci) was not performed and no treatment was used.
- Group 2: Laminectomy and acute trauma (sci) were performed to the 8 rats in the trauma group; no treatment was given.
- Group 3: A single dose of subcutaneous 40 mg/kg adalimumab (Humira, Abbott Laboratories, North Chicago, IL, USA) was administered right after laminectomy and acute trauma (sci) to the 8 rats.
- Group 4: A single dose of 30 mg/kg intravenous methylprednisolone (Prednol, Mustafa Nevzat, Turkey) was administered right after laminectomy and acute trauma (sci) to the 8 rats.
- Group 5: Single doses of 40 mg/kg adalimumab and intravenous 30 mg/kg methylprednisolone were administered together right after laminectomy and acute trauma (sci) to the 8 rats.

Anesthesia and Surgical Procedure

The animals were kept at 18-21°C under constant laboratory conditions consistent with a biorhythm with a 12-hour light-dark cycle and were allowed free access to food and water. General anesthesia was ensured with an intramuscular injection of 5 mg/kg ketamine hydrochloride (Ketalar, Pfizer, Istanbul, Turkey) and 70 mg/kg xylazine (Rompun, Bayer, Istanbul, Turkey). Rats under anesthesia were secured in the prone position using all four extremities. Intramuscular cefotaxime (Bilim Pharmaceuticals, Beyoğlu, İstanbul) was administered at a dose of 40 mg/kg prophylactically 30 minutes before the surgical procedure. The entire dorsal midline was shaved and surface sterilization was provided with polivinylpyrolidone iodine (Polypod®, 10% solution, Drogsan İlaç Sanayi, Ankara, Turkey). The midline incision was performed with aseptic technique along the T5 to T12 spinal processes. The paravertebral muscles were dissected from the T7 to the T10 vertebrae. Once the vertebral column between T7 and T10 was exposed, total laminectomy was performed with a surgical microclamp. The dura was left intact. An aneurysm clip (Yaşargil, FE 721, Aesculap, Germany) with a closure strength 70 g was used for 1 minute to create spinal cord injury in all groups except group 1 (Figure 1). Paraplegia was observed in all rats in groups 2-5 where trauma was created.
Only laminectomy was performed for the 8 rats in group 1. The 8 rats in group 2 underwent laminectomy and trauma (sci) but no treatment was administered. The 8 rats in group 3 were administered a single dose of 40 mg/kg adalimumab right after laminectomy and trauma (sci). The 8 rats in group 4 were administered a single dose of 30 mg/kg methylprednisolone right after laminectomy and trauma (sci). The 8 rats in group 5 were administered single doses of 40 mg/kg adalimumab and intravenous 30 mg/kg methylprednisolone. The incisions were closed with primary sutures after the surgery. The animals were provided food and water and kept in a temperature-controlled room until the end of the experimental protocol. Motor strength and the inclined plane test were evaluated in all rats at 24 hours and 3, 5 and 7 days after trauma. Sedation was provided with intramuscular ketamine and xylazine at the end of the 7th day and blood samples were obtained to determine plasma MDA, IL-1β, IL-6 and TNF-α levels before the rats were sacrificed with the administration of pentobarbital at an excessive dose. The spinal cords were excised at a length of 2 cm at the area of injury (1 cm rostral and 1 cm caudal) and sections were obtained for histopathological study.

Biochemical Analysis

The plasma MDA level of the rats in the control and trauma groups was studied according to the method described by Draper and Hadley (16). Plasma levels were measured in nmol/ml with this method based on the measurement of the intensity of the mixture formed by the interaction of MDA, which is a lipid peroxidation product, and thiobarbituric acid with a spectrophotometer (Beckman Coulter) at a wavelength of 532 nm.

Serum concentrations of the inflammatory mediators (IL-1β, IL-6 and TNF-α) were measured in picograms per milliliter (pg/mL) with the Bio Elisa Reader Eix800 (BioTek Instruments Inc., Winooski, VT) ELISA (enzyme-linked immunosorbent assay) analysis (using ELISA kits (Bender MedSystems Gmbh, Vienna, Austria) designed for rats).

Histopathological Analysis

Anesthesia was ensured with the injection of a ketamine and xylazeline solution at the end of the seventh day and samples were obtained for serum MDA, IL-1β, IL-6 and TNF-α measurements. The skin sutures were then removed and the paravertebral muscles pulled aside. A cord segment 2 cm in length was separated 1 cm rostral and 1 cm caudal from the trauma region of the spinal cord. All samples were fixed in 10% neutral buffered formalin, embedded in paraffin, and 5 µm thick profiles obtained with a microtome. The tissue sections were stained with H&E and evaluated under an Olympus BX-51 light microscope using a semi-quantitative grading scale (Table I) (80).

A total score between 0 and 12 was calculated according to the semi-quantitative grading scale as follows:

- 0 to 3 points (Grade 1) indicated minimal bleeding and necrosis.
- 4 to 7 points (Grade 2) indicated moderate tissue damage.
- 8 to 12 points (Grade 3) indicated severe tissue damage.

Table I: Semi-Quantitative Grading Method

<table>
<thead>
<tr>
<th>Histopathological examination</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td><strong>Edema</strong></td>
<td></td>
</tr>
<tr>
<td>No edematous tissue</td>
<td>0</td>
</tr>
<tr>
<td>Minimal edema</td>
<td>1</td>
</tr>
<tr>
<td>Moderate edema</td>
<td>2</td>
</tr>
<tr>
<td>Heavy edema</td>
<td>3</td>
</tr>
<tr>
<td><strong>Tissue necrosis</strong></td>
<td></td>
</tr>
<tr>
<td>No necrotic tissue</td>
<td>0</td>
</tr>
<tr>
<td>1%–10% necrosis</td>
<td>1</td>
</tr>
<tr>
<td>1%–25% necrosis</td>
<td>2</td>
</tr>
<tr>
<td>Necrosis &gt;25%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>No bleeding</td>
<td>0</td>
</tr>
<tr>
<td>Minimal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>3</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>No inflammatory cells</td>
<td>0</td>
</tr>
<tr>
<td>Few and focal cells</td>
<td>1</td>
</tr>
<tr>
<td>More cells</td>
<td>2</td>
</tr>
<tr>
<td>Abscess formation</td>
<td>3</td>
</tr>
</tbody>
</table>

Inclined Plane Test

The functional improvement of the rats was evaluated using the inclined area (inclined plane) method identified by Rivlin and Tator that is commonly used in experimental acute spinal
cord injuries (61). The rat was placed on a smooth-surfaced plane placed parallel to the floor. The plane was then lifted from the unfixed side and the inclination was increased. The highest angle the animal could stand on the plane for 5 seconds without falling was accepted as the inclined plane angle. The inclined plane test was applied to the rats in all groups 24 hours and 3, 5 and 7 days after the surgical procedure.

Clinical Motor Examination
Open-field behavior was assessed and scored with the Modified Tarlov’s Grading Scale: 1: No movement, 2: minimal hindlimb movement but unable to stand, 3: able to stand but unable to walk, 4: able to walk with mild spasticity or incoordination of the hindlimb, 5: normal motor function) as proposed by Cheng et al. (10). The mean of the evaluator scores was accepted as the final score of the rat.

Statistical Analysis
The SPSS 15 (version 15.0; SPSS Inc., Evanston, IL, USA) program was used to evaluate the findings of our study. The Mann-Whitney U test was used for the evaluation of non-parametric numerical data, and the Pearson Chi-square test for the comparison of categorical data. All data are presented as mean ± standard error (SE). A p value less than 0.05 was accepted as statistically significant.

■ RESULTS

Biochemical Results
Plasma levels of the groups are presented in Table II. There was a statistically significant increase in all 4 mediators (MDA, IL-1β, IL-6 and TNF-α) in the trauma group (group 2) compared to the sham group (p< 0.05). There was a statistically significant decrease in all 4 mediators between the trauma group and the treated groups 3, 4 and 5 (p< 0.05). The concurrent administration of adalimumab and methylprednisolone created no statistically significant decrease in the MDA level compared to separate administration while the decrease in the IL-1β, IL-6 and TNF-α levels was quite significant (p< 0.05).

Histopathological Results
Histopathological results have been presented in Table III and the histopathological photographs of the groups are shown in Figures 2-6.

According to the semi-quantitative grading system, the total score was 9.26 (grade 3) in the trauma group, 5.75 (grade 2) in the adalimumab group, 5.51 (grade 2) in the methylprednisolone group and 4.76 (grade 2) in the adalimumab + methylprednisolone group. Statistical analysis with Pearson’s Chi-square test showed that the best results were in group 5 where both drugs had been administered together when compared to the trauma group (group 2) although not statistically significant (p=0.076). There was no difference regarding edema and bleeding between the trauma group (group 2) and the treatment groups 3, 4 and 4. However, there was a statistically significant difference between necrosis and inflammation the trauma group (group 2) and the treatment groups 3, 4 and 5 (p< 0.05).

Evaluation of the Inclined Plane Test
Inclined plane levels are presented in Table IV. There was a statistically significant decrease in the sham group compared to the trauma group (p< 0.05). There was a statistically significant increase in treatment groups 3, 4 and 5 compared to the trauma group (p< 0.05). There was no difference between administering the two drugs together compared to

<table>
<thead>
<tr>
<th>Table II: Biochemical Values of the Groups in Plasma. Values are Expressed as a Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>1 (sham)</td>
</tr>
<tr>
<td>2 (trauma)</td>
</tr>
<tr>
<td>3 (adalimumab)</td>
</tr>
<tr>
<td>4 (methylprednisolone)</td>
</tr>
<tr>
<td>5 (adalimumab+ methylprednisolone)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table III: The Histopathological Evaluation Scores of the Groups. Values are Expressed as a Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>1 (sham)</td>
</tr>
<tr>
<td>2 (trauma)</td>
</tr>
<tr>
<td>3 (adalimumab)</td>
</tr>
<tr>
<td>4 (methylprednisolone)</td>
</tr>
<tr>
<td>5 (adalimumab + methylprednisolone)</td>
</tr>
</tbody>
</table>
motor evaluation results in the trauma group administered adalimumab (group 3) was close to statistical significance (7th day, p=0.053). The administration of both drugs together showed a statistically significant difference on the 5th and 7th days compared to separate administration (p< 0.05).

Evaluation of Motor Strength
Motor strength evaluation results are presented in Table V. There was a statistically significant decrease in the trauma group compared to the sham group (p< 0.05). The 7th day motor evaluation results in the trauma group administered adalimumab (group 3) was close to statistical significance (7th day, p=0.053). The administration of both drugs together showed a statistically significant difference on the 5th and 7th days compared to separate administration (p< 0.05).

Figure 2: Sham group. Normal histomorphology in the spinal cord (Left, hematoxylin-eosin (H&E) x40; Right, (H&E) x100).

Figure 3: Trauma group (untreated group). Severe hemorrhage and necrosis in the spinal cord (Left, (H&E) x40; Right, (H&E) x100) (Grade 3).

Figure 4: Adalimumab group. Mild hemorrhage in the spinal cord (Left, (H&E) x40; Right, (H&E) x100) (Grade 2).
Table IV: Inclined Plane Results for the 5 Groups. Values are Expressed as a Mean ± SD

<table>
<thead>
<tr>
<th>Group</th>
<th>24 hours</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (sham)</td>
<td>64.37±1.408</td>
<td>64.25±1.164</td>
<td>64.25±1.281</td>
<td>64.37±1.187</td>
</tr>
<tr>
<td>2 (trauma)</td>
<td>34.25±1.669</td>
<td>34.50±2.070</td>
<td>35.00±2.725</td>
<td>34.125±2.587</td>
</tr>
<tr>
<td>3 (adalimumab)</td>
<td>42.50±2.070</td>
<td>44.50±1.603</td>
<td>47.50±2.203</td>
<td>49.50±2.203</td>
</tr>
<tr>
<td>4 (methylprednisolone)</td>
<td>42.00±2.726</td>
<td>43.00±2.203</td>
<td>46.00±2.000</td>
<td>47.50±2.070</td>
</tr>
<tr>
<td>5 (adalimumab+ methylprednisolone)</td>
<td>44.50±1.852</td>
<td>47.00±2.267</td>
<td>50.50±2.203</td>
<td>54.00±2.267</td>
</tr>
</tbody>
</table>

Table V: Motor Scores in the 5 Groups. Values are Expressed as a Mean ± SD

<table>
<thead>
<tr>
<th>Group</th>
<th>24 hours</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (sham)</td>
<td>5.00±0.00</td>
<td>5.00±0.00</td>
<td>5.00±0.00</td>
<td>5.00±0.00</td>
</tr>
<tr>
<td>2 (trauma)</td>
<td>1.25±0.463</td>
<td>1.25±0.463</td>
<td>1.25±0.463</td>
<td>1.25±0.463</td>
</tr>
<tr>
<td>3 (adalimumab)</td>
<td>1.38±0.518</td>
<td>1.38±0.518</td>
<td>1.63±0.518</td>
<td>1.75±0.463</td>
</tr>
<tr>
<td>4 (methylprednisolone)</td>
<td>1.38±0.518</td>
<td>1.38±0.518</td>
<td>1.50±0.535</td>
<td>1.50±0.535</td>
</tr>
<tr>
<td>5 (adalimumab+ methylprednisolone)</td>
<td>1.63±0.518</td>
<td>1.75±0.707</td>
<td>1.88±0.641</td>
<td>2.13±0.641</td>
</tr>
</tbody>
</table>

Figure 5: Methylprednisolone group. Mild to moderate hemorrhage and some necrosis foci in the spinal cord (Left, (H&E) x40; Right, (H&E) x200) (Grade 2).

Figure 6: Adalimumab and Methylprednisolone group. Minimal bleeding and minimal necrosis are seen in the spinal cord section. (Left, (H&E) x40; Right, (H&E) x200) (Grade 2).
DISCUSSION

The primary injury in traumatic spinal cord injuries occurs at the time of trauma (72). Bleeding, edema, axonal and neuronal necrosis and cyst formation are seen together with pathological changes such as demyelination followed by infarction after acute injury (1, 35, 72). There is as yet no specific pharmacological treatment to prevent primary spinal cord injury. Secondary spinal cord injury is the damage occurring within hours as a result of the metabolic, biochemical and pathophysiological factors due to the primary injury (3, 18, 70).

The factors that play a role in this progressive process have not been fully elucidated. In addition to excessive release of glutamate and aspartate, intracellular calcium accumulation, activation of the arachidonic acid cascade, activation of various proteases such as caspase phospholipase-endonuclease, and induction of the peroxidation of lipids of free radical origin (30, 41, 78), sympathetic stimulation also contributes to secondary injury mechanisms through altered blood flow and changes in microvascular permeability although the mechanism is not fully understood (4, 14). Rapid neutrophil migration occurs to the injured region (9). The antioxidant and oxidant systems of the organism are normally in balance. When this balance is disturbed in favor of the oxidants, leucocytes produce inflammatory mediators (bradykinin, prostaglandin, leukotriene, platelet activating factor, serotonin, the adhesion molecule P-selectin, interleukin β, IL-6 and TNF-α) and free oxygen radicals (17, 73). The central nervous system is mostly formed of lipids and the lipid peroxidation caused by free radicals can therefore cause serious damage here (64).

TNF-α is a cytokine with pro-inflammatory and immunoregulatory characteristics. The biological half-life of TNF-α is short and its level increases in the damaged cord area within the first few hours after spinal cord trauma, in the cerebrospinal fluid (CSF) after a couple of hours, and in the serum with the level proportional to the severity of the damage (5, 78, 79). Yuji and Kenji developed an experimental spinal cord trauma in rats and found TNF-α to increase and reach peak values in damaged tissue 4 hours later (82). TNF-α facilitated the initiation of a local immune reaction in nerves. This cytokine causes damage in the blood-nerve barrier and has a cytotoxic effect on the vascular endothelium and increases vascular permeability (58, 66). It therefore facilitates the passage of factors in the circulation such as immunoglobulins, cytokines and complements to the nerve tissue (31, 74). TNF-α shows a myelotoxic effect by stimulating the local macrophages as it increases the release of inflammatory mediators and phagocytosis (44). IL-6 is the most effective stimulant of acute phase reactions in the liver. Mononuclear phagocytic cells, fibroblasts, endothelial cells, B and T lymphocytes, glial cells and bone marrow stroma cells are the sources of IL-6 that plays an important role in defense mechanisms by regulating the immune response, acute phase reactions and hematopoiesis. Its release starts after TNF-α and IL-1α following trauma. It is found in the serum a couple of hours after trauma and stays in the circulation for a few days. TNF-α, IL-6 and IL1β levels increase proportionally to the severity of the trauma after spinal cord injuries and this increase is related to histopathological damage such as cell death and inflammation (36, 69, 78, 79) as well as persistent motor dysfunction (26, 32, 68).

Many investigators are working on developing different methods to simulate acute spinal cord injury pathophysiological mechanisms in order to correct neurological functions (72). Although many pharmacological agents have been tried for such injuries, none of them has been accepted for clinical use except methylprednisolone (12, 50). The mechanism of the neuroprotective effect of methylprednisolone is not known but it decreases lipid peroxidation, stabilizes intracellular and extracellular Ca²⁺ flow, increases spinal blood flow, decreases Na⁺ and water retention of the lesion and prevents K⁺ loss when given at an early stage in spinal cord injury. It has anti-edema and antioxidant effects (6, 27-29, 52, 70, 83). It is known to decrease TNF-α and IL-6 production (24). The NASCIS-II study showed that the dose-dependent antioxidant effect of methylprednisolone was maximum at a dose of 30 mg/kg while the harmful effects started after 60 mg/kg; methylprednisolone given within the first 8 hours provided better neurological recovery in long-term follow-up (7). The NASCIS-III study aimed to determine how long methylprednisolone treatment should last and reported that treatment lasting more than 24 hours did not make a neurological change in patients who were started methylprednisolone within the first 3 hours after the injury while prolongation of methylprednisolone treatment that was started within 3-8 hours after the injury to 48 hours increased neurological recovery (8). However, many clinics are now abandoning the use of methylprednisolone in clinical spinal cord trauma. Plasma MDA levels increase in spinal cord injury (11, 45, 48, 49). A significant decrease in MDA levels has been shown to be present following the administration of methylprednisolone for the treatment of spinal cord compression injury (46).

Adalimumab (Humira®) is a human monoclonal TNF-α antibody drug and blocks the effects of TNF-α. It is used successfully for the treatment of disorders such as Crohn’s disease, ulcerative colitis, psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis. Successful results can be obtained with 40 mg/kg subcutaneously every 2 weeks. It specifically blocks the interaction of the p55 and p75 TNF receptor surface and TNF-α (25). Side effects include development of motor neuropathy characterized by transmission block (51, 53, 54, 67), local injection site reactions, and secondary infective activations including fungal infections and tuberculosis. It can rarely cause lymphoma, lupus-like syndrome, cytopenia, mononeuritis multiplex, acute phrenic neuropathy and multiple sclerosis. It should be used carefully in patients at risk as it can cause pancytopenia and increase certain liver transaminases (2, 51, 63). Infliximab is another anti-TNF agent that has been tried in a spinal cord injury model and shown to have neuroprotective effects (47).

CONCLUSION

Adalimumab is as effective as methylprednisolone for clinical, histopathological and biochemical recovery in compressive spinal cord injuries in rats. A positive synergistic effect was seen in the late stage (day 5 and 7 in particular) of trauma.
regarding the levels of biochemical markers (except MDA), inclined plane levels and motor strength evaluations with the administration of these two drugs together and the difference in histopathological results was close to significance. However, further studies with different and repeated doses of adalimumab in addition to functional, behavioral and biochemical analyses are needed.

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